UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,828	01/24/2002	Xianqiang Li	26757-707	4192

21971 7590 08/11/2006

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,828	LI ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1/10/06* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed May 22, 2006 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 1-22 were pending. Applicants amended claims 1-22. No claims were added or canceled. Therefore, claims 1-22 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. The objection to the abstract is withdrawn in view of Applicants' submission. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

5. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. (WO 00/04196) (Date of Patent is **January 27, 2000**) (see 3/11/04 IDS) and Morris et al. (US Patent No. 6,458,530)(Filing Date is **April 4, 1996**) (of record).

For ***claim 1***, Kauffman et al. (see entire document) disclose "cis acting nucleic acid elements and methods of use" (e.g., see Kauffman et al., title and abstract), which

reads on the claimed invention. For example, Kauffman et al. disclose a library of nucleic acid constructs, each construct comprising a cis element sequence comprising one or more copies of a cis element to which a transcription factor is known to bind (e.g., see claim 38, A plurality of isolated nucleic acid molecule [i.e., a library], each isolated nucleic acid molecule comprising one or more cis acting nucleic acid elements"; see also page 1, lines 29-30, "As an example, regulatory proteins called 'transcription factors' bind to cis acting nucleic acid elements"; see also page 2, line 5; see also page 14, last paragraph; see also page 9, paragraph 2; see also pages 5-6). Kauffman et al. also disclose variation within the cis element sequence (e.g., see page 13, paragraph 1, "As an example, a population that includes all possible molecules of between 5 and 20 nucleotides in length, including each of the four naturally occurring nucleotides at each position, would have approximately ... 10^{13} different nucleic acid molecules. Such a population ... inherently includes all [i.e., known and unknown] possible cis acting nucleic acid elements of up to about 20 nucleotides in length"; see also page 8, first full paragraph; see also page 11, last paragraph; see also page 50, first full paragraph; see also page 22, paragraph 1, "The isolated nucleic acid molecules or the nucleic acid binding factors, or both ... can be biased populations that include cis acting nucleic acid elements ... that are known."). Kauffman et al. also disclose a promoter sequence 3' relative to the cis element sequence (e.g., see page 9, last paragraph, "A cis acting nucleic acid element can be localized within the nucleic acid sequence it regulates, or upstream or downstream thereof"; see also page 3, paragraph 1). Kauffman et al. also disclose a reporter sequence that is 3' relative to the promoter sequence (e.g., page 14, first full paragraph, "If desired,

some or all of the isolated nucleic acid molecules can ... be flanked at one or both ends [i.e., both 3' and 5'] by ... detectable sequences [i.e., reporter molecules]"; see also paragraph bridging pages 50-51, "... a plurality of isolated nucleic acid molecules containing cis acting nucleic acid elements can be ... enhancers and promoters ... or any other set of nucleic acid cis acting elements"). Finally, Kauffman et al. also disclose cis element sequences that "correspond" to a given reporter sequence within the library of nucleic acid constructs (e.g., see page 14, first full paragraph; see also paragraph 19, lines 13-14; see also page 34, middle paragraph; see also page 35, paragraphs 1-3; see also page 60 paragraph 1 which disclose numerous methods of detection using reporter sequences that "correspond" to the cis element i.e., allow identification of the cis element).

Finally, Applicants' newly added limitations (e.g., "transfected into a cell sample", "reporter sequences are transcribed in the cell sample ...") have not been afforded any patentable weight because these limitations represent mere "intended use" language that does not impart any structural differences to the claimed library of nucleic acid constructs. See MPEP § 2111.03, "Intended use recitation and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re

Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963).

For ***claim 2-3***, Kauffman et al. disclose the use of conserved priming sequences (e.g., see page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can include, or be flanked at one or both ends by, known sequences, such as sequences homologous to oligonucleotide primers for the polymerase chain reaction (PCR); see also page 25, last paragraph; see also page 33, first paragraph").

For ***claims 4-7***, Kauffman et al. disclose 10^{13} different cis elements (e.g., see page 13, line 25).

For ***claims 8-10***, Kauffman et al. disclose at least two copies of the cis element (e.g., see claim 38, "A plurality of isolated nucleic acid molecules, each isolated nucleic acid molecule comprising one or more [i.e., two, three, four, etc.] cis acting nucleic acid elements"; see also page 57, lines 24-25).

For ***claims 11-13***, Kauffman et al. disclose cis elements with a length between 5 and 50 base pairs (e.g., see page 10, first full paragraph, "A cis acting nucleic acid element is generally from about 4 to about 100 nucleotides in length, and is more typically from about 6 to about 25 nucleotides in length").

For ***claim 20***, Kauffman et al. disclose different reporter sequences that encode different reporter proteins (e.g., see page 3, paragraph 1; see also page 47, paragraph 1; see also column 6, paragraph 3, "see column 3, lines 46-53, "The methods are advantageous in providing a means for simultaneously identifying nucleic acid binding factors that modulate a genetic activity of a plurality of nucleic acids").

The prior art teaching of Kauffman et al. differs from the claimed invention as follows:

For ***claim 1***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the use of a variable region within the reporter sequence.

For ***claims 14-19***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the size of the variable sequence in the reporter e.g., at least 14 bases in length (see claim 14).

For ***claims 21-22***, the prior art teachings of Kauffman et al. do not explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see column 23, line 48).

However, Morris et al. teach the following limitations that are deficient in Kauffman et al.:

For ***claims 1 and 14-19***, Morris et al. (see entire document) disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, both Morris et al. and Kauffman et al. do not explicitly state that a

stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid library as taught by Kauffman et al. because Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. i.e., the references represent analogous art (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening

embodiments disclosed by Kauffman. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS™ array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS™ array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Kauffman et al. teach general "expression" methods that can used to create the libraries including recombinant DNA and optional PCR techniques (e.g., see Kauffman et al., column 15, last paragraph; see also Morris, column 3, paragraph 2).

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that Kauffman et al. do not teach all of the claimed limitations and that Morris et al. fail to remedy this deficiency. Specifically, Applicants reiterate their previous arguments with respect to the "known" versus "unknown" sequences. In addition, Applicants state that the references do not disclose variable cis elements and variable reporter sequences

(e.g., see 5/22/06 Response, page 6, paragraph 2).

[2] Applicants argue that there is no motivation to combine the teaching of Kauffman et al. and Morris et al. to arrive at the present invention arguing that combining the references would somehow defeat the purpose of the Kauffman et al. reference i.e., Applicants' arguments are not entirely clear on this point (e.g., see 5/22/06 Response, page 6, paragraph 3).

[3] Applicants argue, "In addition, Morris et al. focused on selecting tag nucleic acids that "have uniform hybridization characteristics (i.e., similar thermal binding stability to complementary nucleic acids), making the tag sets suitable for detection by VLSIPSTM and other probe arrays ... Thus, linking a variable cis element to a variable tag nucleic acid would not only render the method inoperable due to complication of dual variables, but also defeat the purpose of selecting tags with desirable characteristics ... [thus] one of ordinary skill in the art would not be motivated to modify Kauffmann et al. in view of Morris et al. or vice versa" (e.g., see 5/22/06 Response, pages 6 and 7).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. As previously stated, Kauffman et al. "inherently" disclose all [i.e., both known and unknown] possible cis acting nucleic acid elements up to about 20 nucleotides in length [i.e., that are different]" (e.g., see page 13, paragraph 1, "As an example, a population that includes all possible molecules of between 5 and 20 nucleotides in length, including each of the four naturally occurring nucleotides at each position, would have approximately ... 10^{13} different nucleic acid molecules. Such a population ... inherently includes all possible cis acting nucleic acid elements of up to about 20 nucleotides in length"; see also page 8, first full paragraph; see also page 11, last paragraph; see also page

50, first full paragraph). In addition, Kauffman et al. also disclose the use of "known" biased libraries (e.g., see Kauffmann et al., page 22, paragraph 1, "The isolated nucleic acid molecules or the nucleic acid binding factors, or both ... can be biased populations that include cis acting nucleic acid elements ... that are known.").

In addition, Kauffman et al. also disclose a reporter sequence that is 3' relative to the promoter sequence (e.g., page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can ... be flanked at one or both ends [i.e., both 3' and 5'] by ... detectable sequences [i.e., reporter molecules]"; see also paragraph bridging pages 50-51, "... a plurality of isolated nucleic acid molecules containing cis acting nucleic acid elements can be ... enhancers and promoters ... or any other set of nucleic acid cis acting elements"). Kauffman et al. also disclose different reporter sequences that encode different reporter proteins (e.g., see page 3, paragraph 1; see also page 47, paragraph 1; see also column 6, paragraph 3, "see column 3, lines 46-53, "The methods are advantageous in providing a means for simultaneously identifying nucleic acid binding factors that modulate a genetic activity of a plurality of nucleic acids"). Morris et al. (see entire document) disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

[2] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Here, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would lead a person of skill in the art to the automated nucleic acid chips and associated methods disclosed by Morris et al. because the invention of Morris et al. "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitates "massive parallel analysis" (e.g., see Morris et al., Summary of Invention). Thus, the purpose of finding new cis elements and/or cis element binding factors/inhibitors/drugs has not been "defeated" as purported by Applicants, but "augmented" as set forth above. In addition, the Examiner notes that the Kauffmann et al. reference is not limited to a method for identifying "new" cis elements as purported by Applicants (e.g., see page 42, last paragraph, "The isolated nucleic acid molecules ... in the exemplary methods of identifying therapeutic compounds ... can be biased populations that include cis acting nucleic acid elements ... that are known"; see also Detailed Description of Invention wherein many embodiments are disclosed).

[3] The Examiner respectfully disagrees. First, Applicants' assertion that "complications" would arise from the "dual variables" is entirely unsupported (i.e., no evidence or scientific reasoning is provided) and is also inconsistent with the disclosure of Morris. For example, in order for the nucleic acid sequences disclosed by Morris et al. to function as "tags" they must "necessarily" hybridize to their complementary sequences in the presence of a target sequence (otherwise they wouldn't function as a tag). Thus, the target sequence does not impede

the hybridization as purported. In addition, there is no evidence to suggest that the "cis element target sequence" disclosed by Kauffman et al. would act any differently than the target sequences mentioned above. To the contrary, less complications would be produced because the uniform hybridization techniques decrease "cross hybridization" and thus "reduce ambiguities" in high throughput screening assays (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS^{TM} array").

A person of ordinary skill in the art would also have reasonably expected to be successful because both references disclose the use of "cloning" techniques to produce the nucleic acid libraries (e.g., compare Kauffman et al., page 50, last paragraph, "The plurality can be produced in abundance by, for example, chemical synthesis or by amplification by the polymerase chain reaction" to Morris et al., "Also, because the methods of using the arrays and tags optionally include PCR, LCR and other in vitro amplification techniques for amplifying tag nucleic acids, the kits of the invention optionally include reagents for practicing in vitro amplification methods such as taq polymerase"). Finally, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip).

7. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (WO 00/34435) (Date of Patent is **June 15, 2000**) and Morris et al. (US Patent No. 6,458,530) (Filing Date is **April 4, 1996**) (of record).

For ***claim 1***, Li et al. (see entire document) teach cis-element reporter constructs and uses thereof including "high throughput" screening libraries (e.g., see abstract; see also example 4), which read on the claimed invention. For example, Li et al. disclose a library of nucleic acid constructs (e.g., see figure 4A/B wherein a library of "SEAP" constructs are disclosed including Ap1, HRE, Myc, p53, etc.). Furthermore, Li et al. disclose a cis element sequence comprising one or more copies of a cis element to which a transcription factor is known to bind (e.g., see Li et al., pages 9-10, Example 1, The following cis elements were utilized for constructing cis-acting reporters: NF-kb ... HRE ... Myc ... p53 ... [etc.]"; see also page 10, last paragraph, "In a AP1-SEAP construct, the cis element in the construct contains six copies of AP1 ... In a SRE-SEAP construct, the construct contains three copies of SRE element ... [etc.]"). Li et al. also disclose a library wherein the cis element varies within the library of nucleic acid constructs (e.g., see figure 4 A/B disclosing, for example, Ap1, HRE, Myc, p53, etc.). Li et al. further disclose a promoter sequence 3' relative to the cis element sequence (e.g., see Summary of Invention, "In one embodiment of the present invention, there is provided a cis element-reporter construct comprising a cis element, a reporter gene and a promoter"; see also figures 1-3 showing, for example, 3' orientation of the TK promoter relative to the KB4 cis element; see also Examples). In addition, Li et al. disclose a reporter sequence that is 3' relative to the promoter sequence (e.g., see figures 1-3 showing SEAP, d2EGFP

and luciferase reporters in a 3' position relative to the cis element, respectively; see also Examples). Finally, Li et al. a "correspondence" between each cis element sequence and a given reporter sequence within the library (e.g., see figure 4A/B, wherein the amount of SEAP activity is shown to "correspond" to the type of cis element under various conditions).

Finally, Applicants' newly added limitations (e.g., "transfected into a cell sample", "reporter sequences are transcribed in the cell sample ...") have not been afforded any patentable weight because these limitations represent mere "intended use" language that does not impart any structural differences to the claimed library of nucleic acid constructs. See MPEP § 2111.03, "Intended use recitation and other types of functional language cannot be entirely disregarded. However, in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey 370 F.2d 576, 152 USPQ 235 (CCPA 1967); In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963).

For ***claim 4-5***, Li et al. disclose a library with 33 cis elements (e.g., see Example 2 and figure 4 A/B wherein 6 (AP1) + 3 (SRE) + 3 (CRE) + 3 (GRE) + 3 (HRE) + 4 (NF-kB) + 3 (NFAT) + 6 (myc) + 2 (p53) = 33 cis elements are disclosed).

For ***claims 8-10***, Li et al. disclose a library that contains at least two copies of the

cis element (e.g., see Example 2 and figure 4 A/B wherein the AP1 construct, for example, contains "six" copies).

For ***claims 11-13***, Li et al. disclose, for example, NF-kB with 40 base pairs (e.g., see Li et al., page 9, lines 6-7).

For ***claim 20***, Li et al. disclose different reporter sequences that encode different reporter proteins (e.g., see figures 1-3 disclosing SEAP, d2EGFP and luciferase, respectively).

The prior art teachings of Li et al. differ from the claimed invention as follows:

For ***claim 1***, Li et al. are deficient in that they do not specifically teach the use of a reporter that comprises a variable sequence (e.g., see figure 4 A/B wherein the "same" reporter is used that does not contain a variable sequence).

For ***claims 2-3***, Li et al. fail to disclose "priming sequences" 5' and 3' to the variable sequences.

For ***claims 6-7***, Li et al. fail to disclose a library with at least 50 cis elements. Li et al. only disclose a library of 33 cis elements.

For ***claims 14-19***, Li et al. fail to disclose the size of the variable sequence in the reporter.

For ***claims 21-22***, Li et al. fail to explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see figures and Examples).

However, Morris et al. teach the following limitations that are deficient in Li et al.:

For ***claim 1***, Morris et al. (see entire document) teach disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claims 2-3***, Morris et al. disclose priming sites 5' and 3' to the reporter sequences (e.g., see figure 5 caption, "Tags were amplified using a single pair of primers that are homologous to the common priming sites which flank each tag [i.e., 5' and 3']").

For ***claims 6-7***, Morris et al. disclose "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would render obvious larger numbers of constructs in order to "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate"; see also column 4, first full paragraph, "In preferred embodiments, the set of tag nucleic acids comprises from 100-100,000 tags. Typically, a tag set will include between about 500 and 15,000 tags. Usually, the number of tags in a tag set is between about 5,000 and about 14,000 tags")

For ***claims 14-19***, Morris et al. disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular,

cellular and viral libraries that would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, Morris et al. does not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been *prima facie* obvious to of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid libraries as taught by Li et al. because Morris et al. explicitly state that their sequences can be used to track, for example, recombinant cells in high throughput screening assays (e.g., see Morris et al., "This invention provides sets of nucleic acid tags, arrays of oligonucleotide probes, nucleic acid-tagged sets of recombinant cells ..."), which would encompass the recombinant cells disclosed by Li et

al. (e.g., see Li et al., Example 4, "A set of d2EGFP reporters with different cis-elements were generated, which are used for monitoring different transcription factors. Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug screening"; see also Example 5, "cell clones can be used in cell based high-throughput screening in search of factors involved in cAMP signal transduction pathway"). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate") and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Li et al. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS™ array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of

probe on the VLSIPS™ array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Li et al. teach general "cloning and expression" methods that can used to create the libraries (e.g., see Morris et al., column 20, last paragraph, "Molecular cloning and expression techniques for making biological and synthetic oligonucleotides and nucleic acids are known in the art. A wide variety of cloning and expression and in vitro amplification methods suitable for the construction of nucleic acids are well-known to persons of skill"; see also Li et al., Summary of Invention, "In yet another embodiment of the present invention, there is provided a method of monitoring activation of a transcription factor, comprising the steps of ... transfecting a cell line with the vector; and detecting expression of the reporter gene, wherein expression of the reporter gene indicates activation of the transcription factor").

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Li et al. fails [to] teach or suggest a library of neucleic acid constructs which are transfected into a cell sample" (e.g., see 5/22/06 Response, page 7, second to last paragraph).

[2] Applicants argue, "Li et al. discloses individual constructs containing a cis element and a fixed reporter gene such as the secreted alkaline phosphatase ... Thus, the cell sample in Li et al. contains only a single construct with a cis element and a reporter gene" (e.g., see 5/22/06 Response, page 7, second to last paragraph).

[3] Applicants argue, "Nowhere does Morris et al. teach or suggest a library of nucleic acid constructs transfected into a sample and having both variable cis elements and variable reporter elements (e.g., see 5/22/06 Response, page 7, second to last paragraph).

[4] Applicants argue, "Linking a variable cis element to a variable reporter gene ... would only render the samples incomparable because of the differences in biochemical properties of the reporter proteins" (e.g., see 5/22/06 Response, pages 7 and 8, especially paragraph bridging pages 7 and 8).

This is not found persuasive for the following reasons:

[1] In response to applicant's argument that their library composition is used for "transfecting cell samples" (e.g., see newly amended claim 1), the Examiner notes that a recitation of intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the present case, subsequent transfection into a cell sample would not impart any structural difference to the nucleic acid constructs. In addition, a preamble is generally not afforded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness

but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Here, Applicants' intended use of transfecting said constructs into a cell sample occurs in the preamble and thus is not afforded any patentable weight.

[2] In response to applicant's arguments against the Li et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In addition, Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants describe the Li et al. reference without describing how the language of the claims can be distinguished from this reference.

[3] In response to applicant's arguments against the Morris et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach both variable cis elements and variable reporter sequences. For example, Li et al. disclose a library wherein the cis elements vary (e.g., see figure 4 A/B disclosing, for example, Ap1, HRE, Myc, p53, etc.). In addition, Morris et al. disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for

labeling molecular (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

[4] The Examiner respectfully disagrees. First, Applicants' assertion that the samples would be "incomparable" is entirely unsupported. For example, in order for the nucleic acid sequences disclosed by Morris et al. to function as "tags" they must "necessarily" hybridize to their complementary sequences in the presence of a target sequence (otherwise they wouldn't function as a tag). Thus, the target sequence does not impede hybridization as purported. In addition, there is no evidence to suggest that the "cis element target sequence" disclosed by Li et al. would act any differently than the other target sequences mentioned above (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array ... because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPSTM array"). Furthermore, Morris et al. explicitly state that their sequences can be used to track, for example, recombinant cells in high throughput screening assays (e.g., see Morris et al., "This invention provides sets of nucleic acid tags, arrays of oligonucleotide probes, nucleic acid-tagged sets of recombinant cells ..."), which would encompass the recombinant cells disclosed by Li et al. (e.g., see Li et al., Example 4, "A set of d2EGFP reporters with different cis-elements were generated, which are used for monitoring different transcription factors. Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug

screening"; see also Example 5, "cell clones can be used in cell based high-throughput screening in search of factors involved in cAMP signal transduction pathway").

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
July 28, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER